## REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended pursuant to and consistent with 37 C.F.R. § 1.112, in light of the remarks that follow, is respectfully requested.

### 1. Status of the Claims

Claims 1-13, 45 and 46 are pending. Claims 14-44 are withdrawn.

With the entry of this amendment, Applicants amend claims 1-13, 45, and 46 and introduce new claims 47 and 48. The amendments are made without prejudice to or disclaimer of the canceled subject matter. Applicants reserve the right to pursue the canceled subject matter in a continuation and/or divisional application.

The amendments to claims 1-13, 45, and 46 are supported as follows. The amendment of the claims to "transgenic rodent" is supported at least at page 28, line 2. The amendments to claims 1, 2, 4, and 46 are further supported by the specification at least at page 41, line 27 to page 48. The amendment to claim 9 corrects a grammatical error. Claims 12 and 13 are amended to recite the HBM sequence identifier and are therefore supported at least by all the original as filed claims. Claim 45 has amended the preamble to correspond with that of claim 1; it was also amended to depend from claim 1. New claims 47-48 are supported at least by the claims as originally filed. Accordingly, Applicants assert that no prohibited new matter has been introduced by way of these amendments.

### 2. Notice of Acknowledged Information Disclosure Statements

Applicants acknowledge with appreciation the return of the initialed Information Disclosure Statement PTO-1449 forms previously submitted on June 15, 2005, November 7, 2005, and November 9, 2005.

### 3. Change of Correspondence Address and Revocation and New Power of Attorney

Applicants submit herewith a Change of Correspondence Address and Revocation and New Power of Attorney.

### 4. Withdrawn Rejections Under 35 U.S.C. §§ 101 and 103

Claims 1-5 and 7-13 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-4, 6-8, 10, and 12-15 of copending application No.

10/477,238 ('238). The rejection is now withdrawn. *See* Office Action, pages 2-3. With regard to the withdrawal of this rejection, the Office stated in the Office Action that "the scope of the instant claims are more narrow than that of '238." Applicants clarify for the record that the claims of the '238 patent application and those of the instant application differ as they have different claim limitations. The claims cannot be construed as being "more narrow."

The Office also has withdrawn the rejection of claims 1-13 under 35 U.S.C. § 101. *See* Office Action, page 3.

Applicants acknowledge the withdrawal of the rejection of claims 1-13 under 35 U.S.C. § 103 in view of Applicants' arguments.

## 5. Non-Statutory Type Double Patenting

Claims 1-13 and 45 are newly provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-8, 10-14, and 16 of copending application No. 10/447,238 ("the '238 application"). The Office asserts that ""[b]oth inventions are drawn to a [*sic*] transgenic animals; however, the instant claims transgenic animals are 'non-human vertebrate' animals, while the '238 are to any animal." Office Action, page 4.

Applicants note that the application number is Serial No. 10/477,238 and not 10/447,238. This was confirmed with the Examiner in a telephone conference on March 3, 2006. Additionally, Applicants respectfully request that the provisional rejection be held in abeyance until one of the applications proceeds to allowance. Any action prior to that point would be premature.

## 6. Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-13 remain rejected in modified form, and claims 45 and 46 are newly rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office acknowledges that the specification is enabled for "a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence, SEQ ID NO. 2, encoding human High Bone Mass (HBM) protein, operably linked to a ubiquitous promoter or a bone-specific promoter, stably integrated in its genome, wherein said mouse exhibits an increase in bone mass in more than one parameter selected from among bone density, bone strength, trabecular number, bone size, and bone tissue connectivity." Office Action, page 5.

However, the Office asserts that the specification "does not reasonably provide enablement for a transgenic non-human vertebrate animal comprising a nucleic acid sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at postion [*sic*] 582 of SEQ ID NO. 2 operably linked to any promoter." *Id.* The Office asserts that the specification does not enable one to make and use the invention commensurate with the scope of the claims for reasons of record, June 9, 2005.

Applicants traverse the rejection to the extent that it applies to the claims as amended.

### 6.1 Purported Lack of Enablement for "a transgenic non-human vertebrate animal comprising a nucleic acid sequence comprising at least 15 contiguous nucleotides of SEQ ID NO. 2 including at least the thymine at postion 582 of SEQ ID NO. 2 operably linked to any promoter"

The Office asserts that the claims are not enabled for the above-recited phrase. Without acquiescing as to the merits of the rejection, Applicants have amended the claims to be directed to a sequence encoding a specified polypeptide sequence or its cognate sequence from another animal. Accordingly, withdrawal of the rejection as to this aspect is respectfully requested to be withdrawn, and the claims allowed.

### 6.2 The Specification Supports Transgene Constructs in Other Animals

On page 6 of the Office Action, the Office also seems to assert that "[t]here is no utility for the transgenic mice that comprise the HBM transgene that exhibit no phenotype." Office Action, page 6. The Office then asserts the importance of transgene integration and expression levels of the transgene as being important to the claimed invention. Additionally, the Office asserts that the claims do not indicate a phenotype.

Applicants disagree with the Office's assertions and traverse the rejection as it applies to the claims. First, it would have been evident to one of skill in the art at the time to screen transgenic animals for those that express the desired nucleic acid and corresponding polypeptide. Second, transgenic animal technology and techniques have been around since the 1980's, with books now being available on the topic. *See, e.g.*, STRATEGIES IN TRANSGENIC ANIMAL SCIENCE (Glenn M. Monastersky and James M. Robl eds., American Society for Microbiology Press 1995).

Third, the reliance by the Office on Hammer (1990 *Cell* 63: 1099-1112; cited in the Office Action dated June 9, 2005 on page 16) for the instant invention is misplaced. Hammer was cited for the assertion that a skilled artisan cannot predict that expression of a heterologous protein when expressed in a transgenic animal will result in a predicted phenotype. The Hammer reference related to transgenic mice expressing human HLA-B27 and human β2-microglobulin (hβ2m), which did not develop the human disease of spondyloarthropathies; expression of the genes in the rat did result in spondyloarthropathies in rats. The Office cannot rely on this reference in support of its contention as the instant claims are directed to a different disease and a different gene. Additionally, Applicants have shown that heterologous expression of the human sequence (SEQ ID NO: 4) in mice produces high bone mass in mice. Also, Applicants submit that animal models exist for bone study in rat and mouse and are commonly used. *See* Donald B. Kimmel, "Animal Models in Osteoporosis Research," in PRINCIPLES OF BONE BIOLOGY, 1640-1643, (John P. Bilezikian et al., eds. 2nd ed. California 2002).

Additionally, the Office's general assertion that the claims do not indicate a phenotype is incorrect. Claim 4 recites several parameters from which to choose the phenotype (also claims 6 and 13 which depend therefrom). Claim 9 (recites "wherein the transgenic animal expresses a human HBM protein". Claim 10 recites an animal that expresses and HBM phenotype. Claim 11 depends from claim 10. Claims 12 and 13 have an expressed HBM protein. Claim 1 as amended refers to increased bone density.

On page 6 of the Office Action, the Office asserts that "[w]hile an artisan could take the transgene construct used in the mouse disclosed in the specification and introduce it to other non-human vertebrate animals, the Hammer et al. teachings indicate that transgene constructs do not necessarily have the same biological activities in other species of animals." There is 94% polypeptide sequence identity between the mouse sequence and the human sequence. Hey et al., 1998 "Cloning of a novel member of the low-density lipoprotein receptor family," *Gene* 216, 103-111. Also, the human sequence, when expressed in mice, yields a high bone mass phenotype. Applicants have shown that the mutation responsible for high bone mass occurs in humans and in mice. Applicants have also expressed the human sequence (SEQ ID NO: 4) in mice with an increased in bone mineral density. *See, e.g.,* Figures 23 and 29 and corresponding text in the specification. Accordingly, there is no scientific reasoning why the mutation would not be expected to function in all rodents and in all primates. In view of the working example, and information provided, all non-human transgenic animals are supported. However, without acquiescing as to the merits of this allegation, Applicants have amended the claims to recite "transgenic rodent."

Thus, for at least all the reasons of record as well as those listed above, this aspect of the rejection should be withdrawn from the claims either as amended or as unamended.

### 6.3 Use of Any Promoter

On page 7 of the Office Action, the Office contends that the specification does not enable the use of any promoter. The Office asserts that the claimed invention is directed to a model for a human bone condition and "[n]othing in the art or the specification teaches that HBM has any effect in other tissues other than bone such that an artisan could readily identify the phenotype associated with HBM expression." Id.

First, a skilled artisan at the time would have been expected to use *any promoter appropriate for the selected animal.* As discussed above, the art of making transgenic animals was developed at the time the application was filed. *See* STRATEGIES IN TRANSGENIC ANIMAL SCIENCE.

Regarding the Office's allegation that nothing in the art or the specification teaches that HBM has any effect in tissues other than bone, is incorrect. Applicants discuss in the specification that individuals expressing HBM also have changes in lipid levels. *See* at least original claims, Section XVII, and Figures 7A-B and associated text. *See also,* Magoori et al., 2003 "Hypercholesterolemia, impaired fat tolerance, and advanced atherosclerosis in mice lacking both low density lipoprotein receptor-related protein 5 and apolipoprotein E," *J. Biol. Chem.* 278: 11331-6. Northern blot analysis revealed that LRP5 and HBM is transcribed in human bone tissue as well as numerous other tissues. *See,* specification Figures, 7A-B and associated text. Additionally, LRP5 has been linked to familial exudative vitreoretinopathy, a well-defined inherited disorder of retinal vessel development. *See,* Online Mendelian Inheritance in Man for LRP5 (attached). LRP5 has been shown to play an essential role in eye development (Fujino et al., 2003 "Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion," *Proc. Nat'l Acad. Sci USA* 100: 229-234). Therefore, Applicants request withdrawal of the Office's allegation that HBM expression does not impact other tissues.

### 6.4 "Comprising at least 15 contiguous nucleotides of SEQ ID NO.2 including at least the thymine at position 582 of SEQ ID NO. 2."

In the paragraph bridging pages 7 to 8 of the Office Action, the Office asserts that the limitation indicated above lacked enablement. "No utility can be ascribed to an animal that expresses a part of HBM and has no phenotype." Office Action, page 8. The Office asserts that no utility can be ascribed to an animal expressing part of HBM that has no phenotype. The Office additionally argued that the phrase encompassed antisense strands, which the Office asserted were not enabled by the specification. Office Action, page 8.

First, Applicants point out that no rejection under 35 U.S.C. § 101 has been made by the Office. Accordingly, if such a rejection is made, Applicants assert that it would constitute a new rejection, and the rejection cannot be made final.

Regarding "comprising at least 15 contiguous nucleotides of SEQ ID NO.2 including at least the thymine at position 582 of SEQ ID NO. 2," without acquiescing to the merit of the Office's arguments with regard to the phrase, Applicants have amended the claims such that the phrase is no longer recited. Accordingly the rejection as to this aspect of the claims should be withdrawn.

### 6.5 Extrachromosomal DNA

On page 9, the Office acknowledges that Applicants' arguments are persuasive regarding the claimed invention including extra-chromosomal DNA, as well as integrated DNA in the animal's chromosome.

### 6.6 Elbrecht Reference

On page 9, the Office cites Elbrecht et al. (1987 *Mol. Cell Biol.* 7: 1276-1279; "Elbrecht") for the proposition that expression levels of a reporter gene are undetectable in their method of generating mice. The Office also asserts that given "the distribution of the vector in the mouse is mosaic, it is unclear whether enough vector is in bone cells, such that the bone cells can express HBM and cause a bone phenotype." *Id.* Accordingly, the Office concludes that the artisan would not have been enabled at the time to make transgenic mice using episomal DNA.

Applicants disagree and traverse this aspect of the rejection. First, Applicants provide working examples of a transgenic rodent with increased bone mass. Second, Elbrecht is a reference from 1987. The instant application has the earliest priority date of May 2001, which is 14 years subsequent to the publication of the Elbrecht article, during which additional promoters and methods of producing transgenic mice evolved. Sufficiency of the specification's disclosure must be judged as of its filing date. *See In re Glass*, 492 F.2d 1228, 1232-33, 181 U.S.P.Q. 31, 34 (C.C.P.A. 1974). Elbrecht is cited for the points that it teaches: (1) that the mice in their study were mosaic for the number of copies of the transgene; (2) that their mice had low copy number of the vector that CAT activity was not detectable. Office Action page 9. Based on the teachings of Elbrecht, the Office asserts that "[t]his would then indicate that an artisan does not know whether this is a viable method for generating the claimed transgenic animals." Office Action, page 9. The Office also argues that because the vector in the mouse is mosaic it is unclear whether enough vector is in the bone cells such that the bone phenotype is observed.

Applicants disagree regarding expression in bone cells and the relevance of Elbrecht generally. Applicants discuss transgenic animals with a phenotype of increased bone mass and provide data thereon. For example, Figure 23 of the specification shows changes in bone mineral density in animals at 9 weeks expressing the HBM variant and a high bone density phenotype over 9 week old wild-type littermate controls. *See,* page 23, specification. Figure 29 shows the effect of bone load on HBM variant expressing mice.

In view of the data within the specification, Applicants assert the Elbrecht article is not relevant and the Office's allegation, in view of such, without foundation. Accordingly, this aspect of the rejection should be withdrawn.

### 6.7 Gene Therapy

On page 10 of the Office Action, the Office states that "[t]he issue of episomal DNA also raises issues that are associated with gene therapy, *i.e.* an expression vector comprising a gene of interest that is administered to a subject. The art teaches that gene therapy is unpredictable." On pages 10-11, the Office cites Somia and Verma (2000 *Nature Reviews: Genetics* 1: 91-99, 91, 1st col. 2nd para.) for support that there is unpredictability in gene therapy, and there in turn unpredictability in generating a transgenic animal that exhibits a bone phenotype. The Office also stated on page 11, that another problem with gene therapy is delivery, and sites to Fenske et al., 2001 *Curr. Opin. Mol. Therapeutics* 3: 153-158.

Applicants assert that this aspect of the enablement rejection is inappropriate. The claims are directed to a transgenic non-human vertebrate animal. These are not methods of treating an animal using gene therapy. Therefore, the arguments regarding unpredictability of gene therapy are misplaced. For purposes of 35 U.S.C. § 112, first paragraph, Applicants have clearly demonstrated how to make the claimed invention, as well as how to use it. *See e.g., In re Wright,* 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993) and *In re Howarth*, 654 F.2d 103, 105, 210 U.S.P.Q. 689, 691 (C.C.P.A. 1981). Moreover, Applicants have reduced the invention to practice.

The assertion that the specification provides no guidance as to any vector that can be used to generate a transgenic animal is wholly inappropriate. Applicants provide data on transgenic animals expressing the HBM phenotype. *See,* Figures 23 and 29. Discussion of preparation of a transgene begins on page 157 of the specification along with the use of different promoters. Discussion of transgene expression *in vitro* is discussed starting on page 159 and *ex vivo* analysis is discussed starting at least at page 168 *et seq.* Production of gene targeted transgenic mice begins on page 162 *et seq.* Confirmation of gene targeting is discussed at least starting on page 166 *et seq.* HBM expression in mice is discussed at least at page 170 *et seq.,* as well as in the examples. Transgene constructions are provided along with characterization of the resultant animals. Accordingly, Applicants assert that more than sufficient guidance is provided in the specification.

The Office digresses with its argument that there may be inefficient gene transfer using viral vectors, unpredictability, and random integration such that the Office concludes that the viral vectors are not enabled. As discussed above, the claims are not directed to gene therapy or a method of treating. They are directed to a transgenic rodents (as amended) comprising a nucleic acid encoding a high bone mass phenotype. An artisan of ordinary skill can take the teachings of the specification as well as what was known in the art at the time (which does not have to be reiterated in detail in a specification) and make the claimed animals. The fact that perhaps some of the transgenic rodents may not express the transgene the same as other animals does not mean that the instant application lacks an enabling disclosure. The skilled artisan would still be able to make the animal and discern which animal has the desired phenotype and use that animal as needed.

Accordingly, Applicants respectfully request withdrawal as to this aspect of the rejection, and allowance of the claims.

### 6.8 The Amended Claims Read on a Transgenic Animal Comprising a Human Bone Cell Transplant

The Office asserts that the amended claims read on a transgenic animal comprising a human bone cell transplant. Office Action, page 11. Applicants have amended the claims for purposes of clarity. The amended claims no longer recite "bone human cells" (*e.g.*, Claim 2). Accordingly, this aspect of the rejection is mooted.

In view of the above arguments and amendments to the claims, Applicants respectfully request withdrawal of the rejection, and allowance of the claims.

## 7. Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-13, 45, and 46 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking descriptive support in the specification. The Office acknowledges that guidance is provided for the transgenic mouse expressing SEQ ID NO. 2 in bone, it does not provide guidance for the breadth of portions or parts of SEQ ID NO. 2. The Office asserts that the claims "broadly encompass a variety of nucleic acid sequences, wherein the nucleic acid sequences are at least 15 contiguous nucleotides of SEQ ID NO.2, including at lest the thymine at position 582 of SEQ ID NO. 2." Office Action, page 14. The Office questions (1) what biological activities the peptides have, (2) that no structures and corresponding biological activity is provided for the peptides, and (3) that the claims also encompass antisense nucleic acids. *Id.*

Without acquiescing as to the merits of the rejection, Applicants have amended the claims such that they no longer recite "comprising at least 15 contiguous nucleotides of SEQ ID NO:2 including at least the thymine at position 582 of SEQ ID NO:2." As the rejection is mooted by amendment to the claims, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

## CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited. In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

If any fees are required or if a Notice of Appeal fee is required to maintain pendency, the Office is asked to charge Deposit Account No. 50-0573. The Office can credit any overpayments to the Account.

Respectfully submitted,
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